through extracellular interaction in their natural environment, or a segment thereof, joined to a transcriptional activation protein DNA binding domain;

b) a nucleotide sequence encoding a second heterologous fusion protein comprising a second peptide of the binding pair, or a segment thereof, joined to a transcriptional activation protein transcriptional activation domain;

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes a transcriptional activation protein; and

c) a luciferase gene activated under positive transcriptional control of the reconstituted transcriptional activation protein.

15. (Amended) A yeast cell comprising:

a) a nucleotide sequence encoding a first heterologous fusion protein comprising a first peptide of a peptide binding pair, or a segment thereof, joined to a transcriptional activation protein DNA binding domain;

b) a nucleotide sequence encoding a second heterologous fusion protein comprising a second peptide of the peptide binding pair, or a segment thereof, joined to a transcriptional activation protein transcriptional activation domain;

wherein the nucleotide sequence encoding either the first or second heterologous fusion protein is present in an effective copy number of at

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least 5 copies per yeast cell and the nucleotide sequence encoding the other heterologous fusion protein is present at a copy number of 1 or 2 per yeast cell;

and

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes a transcriptional activation protein; and

c) a luciferase gene activated under positive transcriptional control of the reconstituted transcriptional activation protein.

16. (Amended) The yeast cell of claim 15 further comprising at least one endogenous nucleotide sequence selected from the group consisting of a nucleotide sequence encoding the transcriptional activation protein DNA binding domain and a nucleotide sequence encoding the transcriptional activation protein transcriptional activation domain, wherein at least one of the endogenous nucleotide sequences is inactivated by mutation or deletion.

29. (Twice amended) A method of detecting the interaction of a first peptide and a second peptide of a peptide binding pair in the presence of a test sample, comprising:

(i) culturing at least one yeast cell, wherein the yeast cell comprises;

a) a nucleotide sequence encoding a first heterologous fusion protein comprising the first peptide of a known peptide binding pair that bind through extracellular interaction in their natural environment, or a segment thereof, joined to a transcriptional activation protein DNA binding domain;

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b) a nucleotide sequence encoding a second heterologous fusion protein comprising the second peptide, or a segment thereof, joined to a transcriptional activation protein transcriptional activation domain;

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes a transcriptional activation protein; and

c) a luciferase gene activated under positive transcriptional control of the reconstituted transcriptional activation protein;

(ii) incubating the test sample with the yeast cell under conditions suitable to detect expression of the luciferase gene; and

(iii) detecting the interaction of the first peptide and the second peptide by determining the level of expression of the luciferase gene.

B3 cont.

43. (Amended) A method for determining whether a test sample interacts with a first or second peptide of a peptide binding pair, comprising:

(i) culturing at least one first yeast cell, wherein the first yeast cell comprises;

a) a nucleotide sequence encoding a first heterologous fusion protein comprising the first peptide or a segment thereof joined to a transcriptional activation protein DNA binding domain;

b) a nucleotide sequence encoding a second heterologous fusion protein comprising the second peptide or a segment thereof joined to a transcriptional activation protein transcriptional activation domain;

B4

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wherein the nucleotide sequence encoding the first heterologous fusion protein is present in an effective copy number of at least 5 copies per yeast cell and the nucleotide sequence encoding the second heterologous fusion protein is present at a copy number of 1 or 2 per yeast cell;

and

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes a transcriptional activation protein; and

c) a luciferase gene activated under positive transcriptional control of the reconstituted transcriptional activation protein;

(ii) culturing at least one second yeast cell, wherein the second yeast cell comprises;

a) a nucleotide sequence encoding the first heterologous fusion protein comprising the first peptide or a segment thereof joined to a transcriptional activation protein DNA binding domain;

b) a nucleotide sequence encoding the second heterologous fusion protein comprising the second peptide or a segment thereof joined to a transcriptional activation protein transcriptional activation domain;

wherein the nucleotide sequence encoding the second heterologous fusion protein is present in an effective copy number of at least 5 copies per yeast cell and the nucleotide sequence encoding the first heterologous fusion protein is present at a copy number of 1 or 2 per yeast cell;

B4 CONT.

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and

wherein binding of the first peptide or segment thereof and the second peptide or segment thereof reconstitutes a transcriptional activation protein; and

c) a luciferase gene activated under positive transcriptional control of the reconstituted transcriptional activation protein;

(iii) incubating a test sample with the first and second yeast cells under conditions suitable to detect luciferase activity;

(iv) detecting the luciferase activity produced by the first and second yeast cells; and

(v) comparing the detected luciferase activity of the first and second yeast cells, wherein lower luciferase activity in one of the yeast cells compared to the other yeast cell indicates that the test sample binds to the heterogeneous fusion protein encoded by the nucleotide sequence present at a copy number of 1 or 2 in that yeast cell exhibiting lower luciferase activity, thereby affecting the binding interaction of the peptide binding pair.

B4 cont.

44. (Twice amended) The method of claim 43 wherein either or both of the first and second yeast cells further comprises at least one endogenous nucleotide sequence selected from the group consisting of a nucleotide sequence encoding the transcriptional activation protein DNA binding domain and a nucleotide sequence encoding the transcriptional activation protein transcriptional activation domain, wherein

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